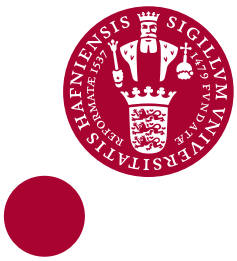

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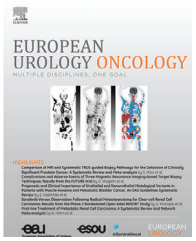

European Association of Urology

Prognostic Association of Prostate-specific Antigen Decline with Clinical Outcomes in Men with Metastatic Castration-resistant Prostate Cancer Treated with Enzalutamide in a Randomized Clinical Trial

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Abstract

Background: In the PREVAIL study, enzalutamide provided significant improvements versus placebo in clinical outcomes in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (mCRPC). The association of post-treatment prostate-specific antigen (PSA) decline with clinical outcomes may provide important prognostic information.

Objective: To evaluate associations between the magnitude of PSA decline from baseline to month 3 and clinical outcomes among enzalutamide recipients.

Design, setting, and participants: This was a post hoc retrospective analysis of PREVAIL, an international, randomized, double-blind, placebo-controlled phase 3 study. Men with mCRPC and no prior chemotherapy from the enzalutamide arm were included (n = 872). Patients were grouped by confirmed maximal PSA decline from baseline to month 3 of treatment (n = 795 evaluable).

Outcome measurements and statistical analysis: Primary outcomes were overall survival and radiographic progression-free survival. Secondary outcomes included PSA progression-free survival, radiographic response, and degradation of Functional Assessment of Cancer Therapy-Prostate score, which were estimated using the Kaplan-Meier method.

Results and limitations: Following 3 mo of enzalutamide treatment, 88% (701/795), 80% (639/795), and 39% (307/795) of patients had postbaseline confirmed maximal PSA declines of ≥30%, ≥50%, and ≥90%, respectively, whereas 12% (94/795) had no confirmed maximal PSA decline or a decline of <30%. Greater degrees of PSA decline within the first 3 mo of enzalutamide treatment were increasingly associated with longer overall survival, time to PSA and radiographic progression,

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higher objective soft-tissue responses, and longer time to quality-of-life deterioration than no PSA decline or declines of <30% from baseline. PSA flares (rise followed by fall) after enzalutamide treatment were rare (<1%).

Conclusions: The magnitude of PSA decline after 3 mo of enzalutamide therapy was strongly associated with better clinical and patient-reported outcomes. This updated prognostic information is of clinical value to this patient population and their health care providers.

Patient summary: We report that decreases in PSA levels are closely linked to better health and survival after 3 mo of enzalutamide treatment in men with metastatic prostate cancer.

The PREVAIL trial is registered at clinicaltrials.gov as NCT01212991.

1. Introduction

Treatment for men with metastatic castration-resistant prostate cancer (mCRPC) has substantially evolved with the use of novel hormonal therapies, and at present enzalutamide or abiraterone acetate with prednisone is recommended before use of cytotoxic chemotherapy [1,2]. These hormonal therapies improve survival and delay radiographic and symptomatic disease progression, but the degree and durability of responses vary.

Serum levels of prostate-specific antigen (PSA), an androgen receptor (AR)-regulated protein, correlate strongly with disease burden and prognosis in the mCRPC setting, and levels decline significantly with AR pathway inhibition [1,3–5]. Docetaxel was the first systemic therapy for which it was demonstrated that declines in PSA are associated with better overall survival (OS) and quality of life (QoL) in mCRPC [3,6]. In these studies, PSA declines following 3 mo of docetaxel were strongly associated with survival and better outcomes, but did not fulfill surrogacy criteria. Although current clinical research guidelines (Prostate Cancer Clinical Trials Working Group 3 [PCWG3]) do not recommend PSA as a surrogate endpoint for regulatory approval, PSA changes along with imaging and patient-reported outcomes may provide critical prognostic information during therapy that justify continuing therapy or considering alternative approaches.

We evaluated PSA declines in the PREVAIL study, in which enzalutamide provided significant improvements versus placebo [1,2,7]. The aim of this post hoc analysis was to characterize the prognostic association between the magnitude of a PSA decline from baseline to month 3 and clinical outcomes. We found that early PSA declines with enzalutamide were highly associated with better long-term clinical outcomes and patient-reported outcomes.

2. Patients and methods

2.1. Study design and conduct

We conducted a post hoc retrospective analysis of the prospective PREVAIL study (NCT01212991; $n = 1717$), an international, randomized, double-blind, placebo-controlled phase 3 trial. The PREVAIL study design and eligibility criteria, as well as baseline characteristics and outcomes, were published previously [1].

Patients were randomized 1:1 to receive oral enzalutamide 160 mg or placebo once daily until intolerance, confirmed radiographic disease progression, or initiation of another therapy for prostate cancer. PREVAIL was stopped after a planned interim survival analysis at 540 reported deaths showed a benefit in favor of enzalutamide (data cutoff September 16, 2013) [1]. Results of the PREVAIL co-primary endpoints of OS and radiographic progression-free survival (rPFS), also used for the current PSA decline analysis, were previously published [1,7]. These patients had CRPC and were either asymptomatic or only mildly symptomatic. A total of 626 patients (72%) in the enzalutamide group and 532 patients (63%) in the placebo group were alive at the data cutoff date (29% reduction in risk of death; hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.60–0.84; $p < 0.001$) [1,8].

2.2. Analysis of PSA decline

Scheduled PSA measurements were conducted at screening, immediately before the first dose of the study drug, at weeks 13 (month 3), 17, 21, and 25, and every 12 wk thereafter. For this post hoc analysis, men from the enzalutamide arm of PREVAIL were grouped into four categories for the confirmed maximal PSA decline from baseline to month 3 following treatment initiation as follows: no decline or a decline <30%; ≥30% decline; ≥50% decline; and ≥90% decline (Fig. 1).

Confirmation required a PSA decline on one or more consecutive visits after month 3. The best overall PSA decline at any point while on enzalutamide therapy was also summarized without stratification. A PSA flare phenomenon was defined as a documented transient PSA increase or no decline within 3 mo on enzalutamide treatment followed by a decline of ≥30% compared with the pretreatment baseline PSA level at later time points.

2.3. Assessment of radiographic progression

Radiographic disease in soft tissue was evaluated using computed tomography or magnetic resonance imaging and in bone using technetium bone scintigraphy at screening, weeks 9, 17, and 25, and every 12 wk thereafter [1]. Radiographic progression was determined using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST) for soft tissue or criteria adapted from the Prostate Cancer Clinical Trials Working Group 2 for osseous disease [9–11].

Radiographic disease progression in bone (≥2 new lesions on radionuclide bone scan) observed at week 9 required two additional new lesions on a confirmatory scan ≥6 wk later; radiographic disease progression in bone observed after week 9 required persistence of two new lesions on a confirmatory scan ≥6 wk later. rPFS was defined as the time from randomization to the first objective evidence of radiographic disease progression (assessed by blinded independent central review) or death due to any cause within 168 d after treatment

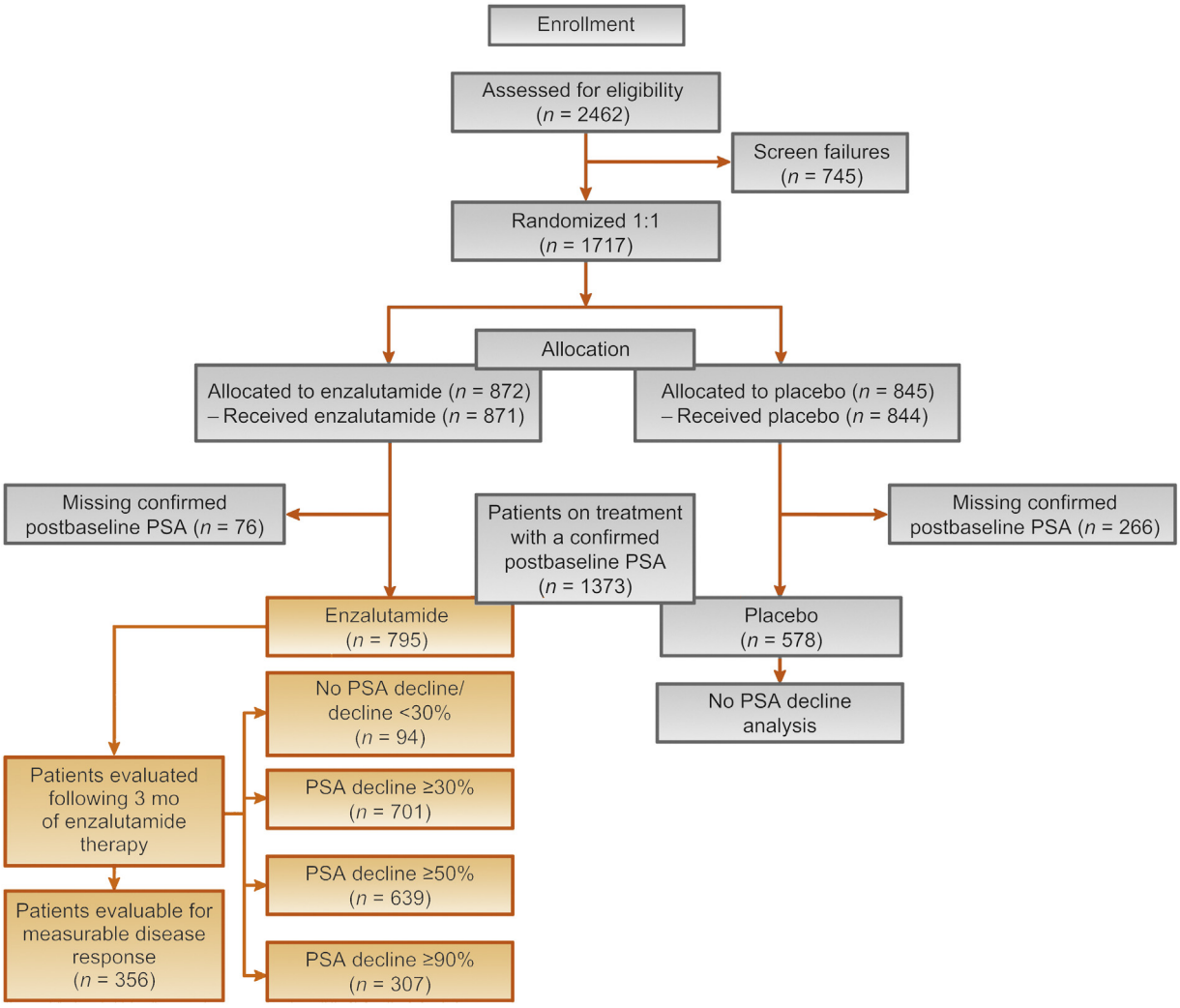


Fig. 1 – CONSORT diagram showing the relationship between the PREVAIL trial population and the subgroups analyzed by prostate-specific antigen (PSA) decline in the enzalutamide arm.

discontinuation, whichever occurred first. OS was defined as time from randomization to death due to any cause.

2.4. *Functional Assessment of Cancer Therapy-Prostate*

The Functional Assessment of Cancer Therapy-Prostate (FACT-P) QoL questionnaire was used to assess patient function in four domains (physical, social/family, emotional, and functional well-being) and global QoL, with higher scores representing better QoL. A validated version of the questionnaire was completed by the patient on day 1, at weeks 5 and 13, and every 12 wk thereafter, and the time from randomization to date of degradation of FACT-P score was evaluated. Degradation in FACT-P score was defined as a $\geq$10-point decrease from baseline in total score. Degradation on individual FACT-P domains was defined as a $\geq$3-point decrease from baseline score for that domain.

2.5. *Analysis of outcomes*

This post hoc analysis was designed to investigate the association between PSA decline by 3 mo and OS, and with the secondary outcomes of rPFS, PSA PFS, RECIST response, and time to FACT-P degradation. Time to best overall PSA decline was the duration from first treatment date to the date of the lowest postbaseline PSA measurement. Estimates of the median and 95% CIs for the time-to-event analyses were determined using the Kaplan-Meier method for OS, rPFS, PSA progression, and FACT-P degradation. The HR was determined using an unstratified Cox regression model (with PSA decline groups as the only covariate) and was relative to the no-decline or decline <30% group. For the HR 95% CIs, an upper limit value of <1.00 indicated benefit in favor of the PSA decline groups. A two-sided Fisher's exact test with a significance level of 0.05 was used to compare the PSA decline groups with the no-decline or decline <30% group for best overall RECIST response. The data cutoff dates were September 16, 2013 for OS, PSA progression, FACT-P degradation, and best overall soft-tissue response, and May 6, 2012 for rPFS. SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA) was used for these analyses.

3. Results

3.1. *PSA metrics in PREVAIL*

The median baseline PSA before treatment was 54 ng/ml (range 0.1–3182 ng/ml) for men treated with enzalutamide (n = 872) [1]. After 3 mo of enzalutamide treatment, a

Table 1 – Outcomes for the enzalutamide arm (*N* = 795)[a] stratified by PSA decline at month 3

Outcome	Maximal confirmed PSA decline from baseline at month 3			
	No decline/decline <30% (*n* = 94/795)	≥30% decline (*n* = 701/795)	≥50% decline (*n* = 639/795)	≥90% decline (*n* = 307/795)
Best objective STR (CR + PR), % (95% CI)[b]	12.0 (4.5–24.3)	70.6 (65.1–75.6)[c]	74.8 (69.2–79.9)[c]	89.7 (82.8–94.6)[c]
Median time to PSA progression, mo (95% CI)	3.7 (3.7–4.6)	13.8 (11.3–14.0)	13.9 (13.8–16.6)	22.5 (16.8–NR)
HR for time to PSA progression (95% CI)	1.0 (reference)	0.17 (0.13–0.22)	0.16 (0.12–0.20)	0.10 (0.08–0.14)
Median rPFS, mo (95% CI)	7.9 (3.7–NR)	NR (13.8–NR)	NR (13.8–NR)	NR (13.8–NR)
HR for rPFS (95% CI)	1.0 (reference)	0.20 (0.13–0.31)	0.17 (0.11–0.27)	0.10 (0.05–0.19)
Median OS, mo (95% CI)	23.1 (17.8–28.0)	32.4 (31.5–NR)	NR (31.5–NR)	NR (NR–NR)
HR for OS (95% CI)	1.0 (reference)	0.31 (0.22–0.42)	0.28 (0.20–0.39)	0.19 (0.12–0.28)

CI = confidence interval; CR = complete response; HR = hazard ratio; NR = not reached; OS = overall survival; PR = partial response; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria In Solid Tumors; rPFS = radiographic progression-free survival; STR = soft-tissue response.
[a] Number of patients at risk at week 13.
[b] Patients with at least one target lesion identified per RECIST version 1.1 at screening are included in this analysis.
[c] $p < 0.001$ versus no PSA decline/PSA decline <30% based on Fisher's exact test.

minority (12%; 94/795) of patients in the enzalutamide arm had no PSA decline or a decline <30%, and 88% (701/795), 80% (639/795), and 39% (307/795) of men had a confirmed maximal PSA decline of ≥30%, ≥50%, and ≥90%, respectively (Fig. 1). PSA flares (rise followed by a fall) after 3 mo of enzalutamide treatment were rare (*n* = 4; <1%). The median time to best overall PSA decline with enzalutamide was 4.6 mo (range 0.8–30.5 mo) for 854 patients who had at least one postbaseline PSA measurement. However, 420 patients of 854 patients (49%) had further PSA declines at month 6 compared with month 3, and 278 patients of 854 patients (33%) had further PSA declines beyond month 6.

3.2. *Prognostic association of PSA decline with clinical outcomes*

Key primary and secondary outcomes with enzalutamide therapy are provided by PSA decline category in Table 1.

Compared with the no-decline or decline <30% group, the groups with PSA declines of ≥30%, ≥50%, and ≥90% within the first 3 mo of enzalutamide treatment had longer times to PSA progression, rPFS, and OS (Fig. 2A–C) and higher objective soft-tissue responses (all $p < 0.001$; Fig. 3). The median time to PSA progression in the no-decline or decline <30% group and the groups with confirmed PSA declines of ≥30%, ≥50%, and ≥90% was 3.7 mo (95% CI 3.7–4.6), 13.8 mo (95% CI 11.3–14.0), 13.9 mo (95% CI 13.8–16.6), and 22.5 mo (95% CI 16.8–not reached [NR]), respectively (Table 1). The median rPFS duration for the no-decline or decline <30% group was 7.9 mo (95% CI 3.7–NR) and had not been reached in the groups with confirmed PSA declines of ≥30%, ≥50%, and ≥90% (Table 1).

The median OS was 23.1 mo (range 17.8–28.0) for the no-decline or decline <30% group and 32.4 mo (range 31.5–NR) for the group with a PSA decline of ≥30%. Median OS was not reached for the groups with confirmed PSA declines of ≥50% and ≥90% (Table 1). The HR for OS was 0.31 (95% CI 0.22–0.42), 0.28 (95% CI 0.20–0.39), and 0.19 (95% CI 0.12–0.28) for the groups with PSA declines of ≥30%, ≥50%, and ≥90%, respectively (Table 1) versus the no-decline or decline <30% group; OS was prolonged in the PSA decline groups compared with the no-decline or decline <30% group. Compared with the no-decline or decline <30% group, groups with a confirmed PSA decline of ≥30%, ≥50%, and ≥90% had a greater probability of objective soft-tissue response, increasing from 12% to 71%, 75%, and 90% (Table 1; Fig. 3). A complete response in soft-tissue metastases was observed in 4%, 24%, 26%, and 45%, respectively, of these patients.

The results for best overall confirmed PSA decline at any time during enzalutamide therapy were similar to those seen after 3 mo of treatment. More specifically, the Kaplan-Meier curves of rPFS and OS show great separations between the PSA decline groups and the no-decline or decline <30% group. The HR for rPFS was 0.18 (95% CI 0.12–0.27), 0.15 (95% CI 0.1–0.23), and 0.07 (95% CI 0.04–0.13) for the groups with declines of ≥30%, ≥50%, and ≥90%, respectively, compared with the no-decline or decline <30% group (Supplementary Fig. 1). The HR (95% CI) for OS was 0.30 (0.22–0.40), 0.27 (0.20–0.37), and 0.18 (0.12–0.26) for the groups with declines of ≥30%, ≥50%, and ≥90%, compared with the no-decline or decline <30% group (Supplementary Fig. 2). Both rPFS and OS were prolonged in the PSA decline groups compared with the no-decline or decline <30% group.

3.3. *Association of PSA decline with QoL*

Declines in PSA were strongly associated with delays in QoL deterioration. Individual Kaplan-Meier curves for time to degradation in FACT-P global QoL domain score are provided in Fig. 4 and corresponding values in Supplementary Table 1. The median time to degradation in FACT-P global QoL domain score was longer in the groups with confirmed PSA declines of ≥30% (13.8 mo, 95% CI 11.2–16.6), ≥50% (14.0 mo, 95% CI 13.6–16.6), and ≥90% (16.5 mo, 95% CI 11.2–24.9) than in the no-decline or decline <30% group (5.6 mo, 95% CI 3.1–8.3). The corresponding HRs for FACT-P global for the PSA decline groups were 0.58 (95% CI 0.43–0.78), 0.56 (95% CI 0.41–0.75), and 0.51 (95% CI 0.37–0.71) when compared with the no-decline or decline <30% group; time to FACT-P degradation was prolonged in the PSA decline groups compared with the no-decline or decline <30% group. The median time to score degradation was also longer for the physical, social/family, emotional, and

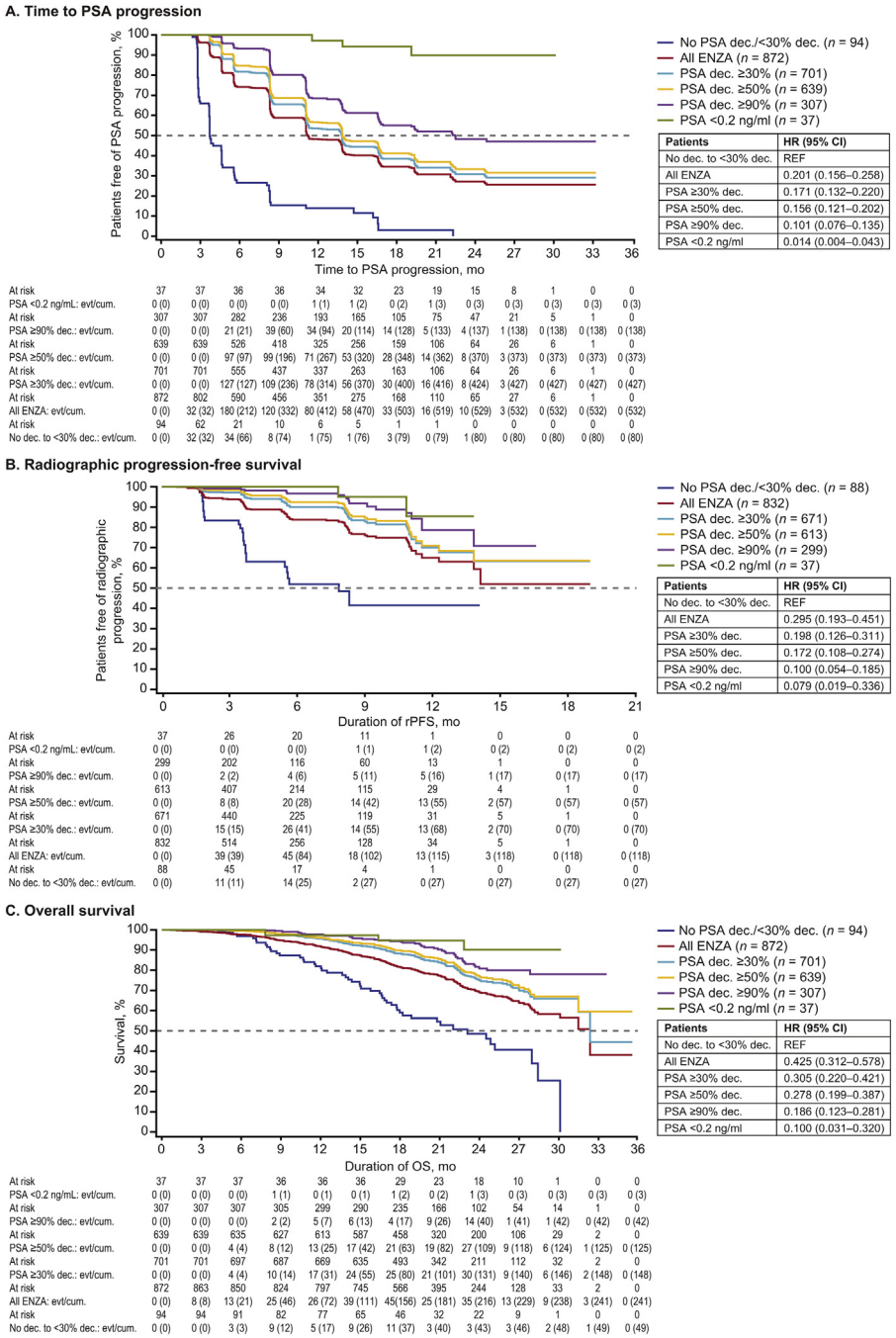


Fig. 2 – Kaplan-Meier plot of (A) time to PSA progression, (B) rPFS, and (C) OS by level of greatest confirmed PSA decline from baseline within the first 3 mo of treatment with enzalutamide. CI = confidence interval; dec. = decline; ENZA = enzalutamide; evt/cum. = events/cumulative events; HR = hazard ratio; OS = overall survival; PSA = prostate-specific antigen; REF = reference; rPFS = radiographic progression-free survival.

functional well-being FACT-P subdomains in the groups with PSA declines of ≥30%, ≥50%, and ≥90% than in the no-decline or decline <30% group (Supplementary Table 1).

4. Discussion

In this post hoc analysis of PREVAIL, we found that the magnitude of post-treatment confirmed maximal PSA declines after 3 mo of therapy was strongly associated with better OS. In addition, PSA declines were strongly associated with radiographic responses, including complete remission of soft-tissue metastases, and delays in PSA and radiographic progression and QoL deterioration. These data provide important prognostic information to health care providers who commonly use AR inhibitors such as enzalutamide to treat patients with mCRPC before chemotherapy. Equally important, a PSA decline of <30% at 3 mo was associated with poor prognosis, a low radiographic

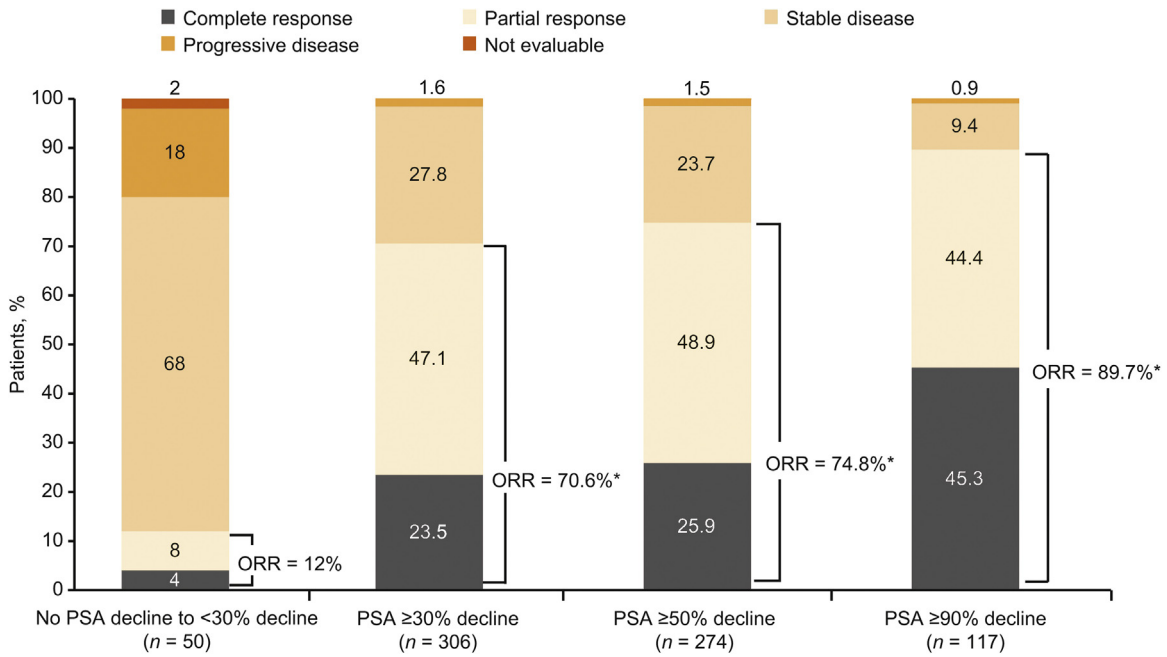
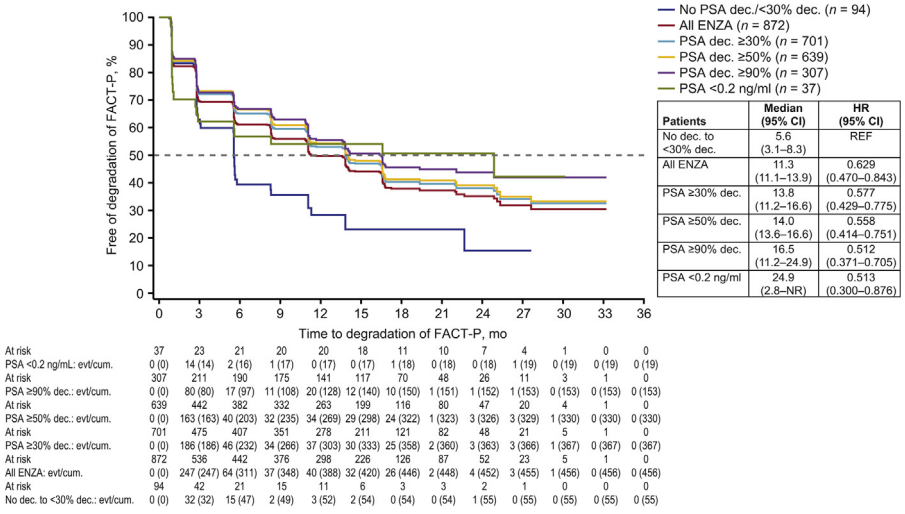


Fig. 3 – Best objective soft-tissue response by level of greatest confirmed PSA decline from baseline within first 3 mo of treatment in enzalutamide arm of PREVAIL (intention to treat patients with measurable disease). ORR = objective response rate; PSA = prostate-specific antigen. *$p < 0.001$ versus no PSA decline/PSA decline <30% according to Fisher's exact test.



Patients	Median (95% CI)	HR (95% CI)
No dec. to <30% dec.	5.6 (3.1–8.3)	REF
All ENZA	11.3 (11.1–13.9)	0.629 (0.470–0.843)
PSA ≥30% dec.	13.8 (11.2–16.6)	0.577 (0.429–0.775)
PSA ≥50% dec.	14.0 (13.6–16.6)	0.558 (0.414–0.751)
PSA ≥90% dec.	16.5 (11.2–24.9)	0.512 (0.371–0.705)
PSA <0.2 ng/ml	24.9 (2.8–NR)	0.513 (0.300–0.876)

At risk	37	23	21	20	20	18	11	10	7	4	1	0	0
PSA <0.2 ng/mL: evt/cum.	0 (0)	14 (14)	2 (16)	1 (17)	0 (17)	0 (17)	1 (18)	0 (18)	0 (18)	1 (19)	0 (19)	0 (19)	0 (19)
At risk	307	211	190	175	141	117	70	48	26	11	3	1	0
PSA ≥90% dec.: evt/cum.	0 (0)	80 (80)	17 (97)	11 (108)	20 (128)	12 (140)	10 (150)	1 (151)	1 (152)	1 (153)	0 (153)	0 (153)	0 (153)
At risk	639	442	382	332	263	199	116	80	47	20	4	1	0
PSA ≥50% dec.: evt/cum.	0 (0)	163 (163)	40 (203)	32 (235)	34 (269)	29 (298)	24 (322)	1 (323)	3 (326)	3 (329)	1 (330)	0 (330)	0 (330)
At risk	701	475	407	351	278	211	121	82	48	21	5	1	0
PSA ≥30% dec.: evt/cum.	0 (0)	186 (186)	46 (232)	34 (266)	37 (303)	30 (333)	25 (358)	2 (360)	3 (363)	3 (366)	1 (367)	0 (367)	0 (367)
At risk	872	536	442	376	298	226	126	87	52	23	5	1	0
All ENZA: evt/cum.	0 (0)	247 (247)	64 (311)	37 (348)	40 (388)	32 (420)	26 (446)	2 (448)	4 (452)	3 (455)	1 (456)	0 (456)	0 (456)
At risk	94	42	21	15	11	6	3	3	2	1	0	0	0
No dec. to <30% dec.: evt/cum.	0 (0)	32 (32)	15 (47)	2 (49)	3 (52)	2 (54)	0 (54)	0 (54)	1 (55)	0 (55)	0 (55)	0 (55)	0 (55)

Fig. 4 – Kaplan-Meier curve for exploratory analysis of time to degradation of the FACT-P global quality of life score among patients treated with enzalutamide by PSA group confirmed at week 13 (intention-to-treat population). CI = confidence interval; dec. = decline; ENZA = enzalutamide; evt/cum. = events/cumulative events; FACT-P = Functional Assessment of Cancer Therapy-Prostate; HR = hazard ratio; NR = not reached; PSA = prostate-specific antigen; REF = reference.

response rate, and short PFS, time to symptom deterioration, and OS.

The strengths of this analysis are the large sample size and the prospective and global multicenter nature of the study cohort, permitting extrapolation of these results to patients in many areas of the world. Second, given the lack of PSA flares after 3 mo of enzalutamide therapy, a rise in PSA after 3 mo of therapy is a likely indicator of worse outcomes with enzalutamide, whereas a decline in PSA following enzalutamide treatment can be reassuring to patients and health care providers that therapy is associated with clinical benefits. Ongoing PSA declines beyond 3 mo were also common, illustrating that further reductions in PSA continue long term in many patients and have prognostic importance regarding clinical outcomes. A lack of a PSA decline of ≥30% within 3 mo was found to be associated with worse outcomes and was identified in 12% (94/795) of patients treated with enzalutamide; thus, close

follow-up with imaging and clinical assessments over time are needed to ensure clinical benefits of continued therapy in these patients. Such patients might benefit from additional or alternative investigational approaches. However, we did observe that 12% of patients in the no-decline or decline <30% group remarkably had a soft-tissue partial or complete response, and 68% of such patients had stabilization of their disease on imaging, illustrating that PSA changes alone should not be used to decide whether to discontinue AR inhibitors such as enzalutamide. Our results extend and confirm similar findings observed in patients with mCRPC receiving enzalutamide after docetaxel in the AFFIRM trial [12], and reflect similar associations of post-treatment PSA declines with better outcomes in men with mCRPC and metastatic hormone-sensitive prostate cancer treated with docetaxel [3,6,13,14]. The PCWG3 guidelines support the continuation of systemic therapy until the patient is no longer clinically benefiting, which may extend beyond isolated PSA or imaging progression criteria [15]. The limitations of this analysis include our focus on enzalutamide. However, prior analyses have also documented clear associations between PSA declines and outcomes in patients treated with docetaxel and abiraterone acetate, but without demonstrating surrogacy for PSA declines for OS [16,17]. In addition, we did not account for confounding of prognostic factors that may be associated with a greater probability of a PSA decline. A separate multivariable analysis [18] demonstrated that baseline prognostic factors and risk groups are highly associated with OS and PFS, as well as confirmed PSA declines. Although PSA declines were confirmed, approximately 10–30% of responding patients still develop radiographic progression within 6–12 mo of therapy despite having had a PSA decline. These findings suggest that PSA declines may be transient in some men, and that disease heterogeneity and resistance mechanisms within the tumor require frequent assessments, including imaging. For example, it was recently reported that nearly 25% of men with mCRPC treated with enzalutamide develop radiographic progression without defined PSA progression [19]. These data, and the observation noted above that some patients experience radiographic responses without substantial PSA declines, illustrate the need for comprehensive radiologic and clinical assessment of patients and their disease status rather than reliance on PSA measurement alone.

5. Conclusions

In conclusion, declines in PSA after 3 mo of enzalutamide therapy are strongly associated with improvements in OS, rPFS, and health-related QoL. The absence of a PSA decline of ≥30% after 3 mo of therapy identifies an important subset of men with particularly poor prognosis, and few of these patients will benefit in the long term despite a short-term period of disease stability, whereas men with more substantial PSA declines experienced longer-term delays in progression and QoL deterioration. These PSA response patterns thus identify men who might benefit from alternative or additional therapies for better outcomes.

Preliminary findings from this study were presented as a poster discussion (Poster 787PD) at the Annual Congress of the European Society for Medical Oncology, September 8–12, 2017, in Madrid, Spain.

Author contributions: Andrew J. Armstrong had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Armstrong, Iversen, Higano, Beer.
Acquisition of data: Armstrong, Higano, Sternberg, Iversen, Beer.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euo.2018.11.005.

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